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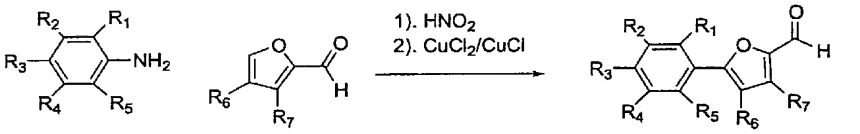
(54) Title: COMMON LIGAND MIMICS: THIAZOLIDINEDIONES AND RHODANINES

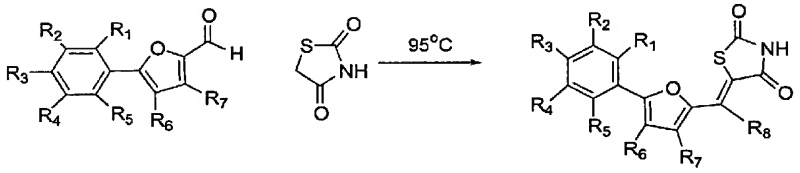


1

2

2-furaldehyde

3a R_3 = COOH
3b R_2 = COOH
3c R_3 = OH
3d R_3 = OH, R_2 = COOMe
3f R_2 = NHAc
3g R_2= OMe, R_3 = OMe



3a R_3 = COOH
3b R_2 = COOH
3c R_3 = OH
3d R_3 = OH, R_2 = COOMe
3f R_2 = NHAc
3g R_2= OMe, R_3 = OMe

4
2,4-thiazolidinedione

5a R_3 = COOH
5b R_2 = COOH
5c R_3 = OH
5d R_3 = OH, R_2 = COOMe
5e R_3 = OH, R_2 = COOH
LiOH
5f R_2 = NHAc
5g R_2 = OMe, R_3 = OMe

(57) Abstract: The present invention provides common ligand mimics that act as common ligands for a receptor family. The present invention also provides bi-ligands containing these common ligand mimics. Bi-ligands of the invention provide enhanced affinity and/or selectivity of ligand binding to a receptor or receptor family through the synergistic action of the common ligand mimic and specificity ligand which compose the bi-ligand. The present invention also provides combinatorial libraries containing the common ligand mimics and bi-ligands of the invention. Further, the present invention provides methods for manufacturing the common ligand mimics and bi-ligands of the invention and methods for assaying the combinatorial libraries of the invention.

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COMMON LIGAND MIMICS: THIAZOLIDINEDIONES AND RHODANINES

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates generally to receptor/ligand interactions and to combinatorial libraries of ligand compounds. The present invention also relates to the manufacture of thiazolidinediones and rhodanines and combinatorial libraries containing such compounds.

BACKGROUND INFORMATION

Two general approaches have traditionally been used for drug discovery: screening for lead compounds and structure-based drug design. Both of these approaches are laborious and time-consuming and often produce compounds that lack the desired affinity or specificity.

Screening for lead compounds involves generating a pool of candidate compounds, often using combinatorial chemistry approaches in which compounds are synthesized by combining chemical groups to generate a large number of diverse candidate compounds that bind to the target or that inhibit binding to the target. The candidate compounds are screened with a drug target of interest to identify lead compounds that bind to the target or inhibit binding to the target. However, the

screening process to identify a lead compound can be laborious and time consuming.

Structure-based drug design is an alternative approach to identifying drug candidates. Structure-based drug design uses three-dimensional structural data of the drug target as a template to model compounds that bind to the drug target and alter its activity. The compounds identified as potential drug candidates using structural modeling are used as lead compounds for the development of drug candidates that exhibit a desired activity toward the drug target.

Identifying compounds using structure-based drug design can be advantageous when compared to the screening approach in that modifications to the compound can often be predicted by modeling studies. However, obtaining structures of relevant drug targets and of drug targets complexed with test compounds is extremely time-consuming and laborious, often taking years to accomplish. The long time period required to obtain structural information useful for developing drug candidates is particularly limiting with regard to the growing number of newly discovered genes, which are potential drug targets, identified in genomics studies.

Despite the time-consuming and laborious nature of these approaches to drug discovery, both screening for lead compounds and structure-based drug design have led to the identification of a number of useful drugs, such as receptor agonists and antagonists. However, many of the drugs identified by these approaches have unwanted

toxicity or side effects. Therefore, there is a need in the art for drugs that have high specificity and reduced toxicity. For example, in addition to binding to the drug target in a pathogenic organism or cancer cell, in some cases the drug also binds to an analogous protein in the patient being treated with the drug, which can result in toxic or unwanted side effects. Therefore, drugs that have high affinity and specificity for a target are particularly useful because administration of a more specific drug at lower dosages will minimize toxicity and side effects.

In addition to drug toxicity and side effects, a number of drugs that were previously highly effective for treating certain diseases have become less effective during prolonged clinical use due to the development of resistance. Drug resistance has become increasingly problematic, particularly with regard to administration of antibiotics. A number of pathogenic organisms have become resistant to several drugs due to prolonged clinical use and, in some cases, have become almost totally resistant to currently available drugs. Furthermore, certain types of cancer develop resistance to cancer therapeutic agents. Therefore, drugs that are refractile to the development of resistance would be particularly desirable for treatment of a variety of diseases.

One approach to developing such drugs is to find compounds that bind to a target protein such as a receptor or enzyme. When such a target protein has two adjacent binding sites, it is especially useful to find

"bi-ligand" drugs that can bind at both sites simultaneously. However, the rapid identification of bi-ligand drugs having the optimum combination of affinity and specificity has been difficult. Bi-ligand drug candidates have been identified using rational drug design, but previous methods are time-consuming and require a precise knowledge of structural features of the receptor. Recent advances in nuclear magnetic spectroscopy (NMR) have allowed the determination of the three-dimensional interactions between a ligand and a receptor in a few instances. However, these efforts have been limited by the size of the receptor and can take years to map and analyze the complete structure of the complexes of receptor and ligand.

Thus, there exists a need for compounds that bind to multiple members of a receptor family. There is also a need for receptor bi-ligands containing such compounds coupled to ligands having a high specificity for the receptor.

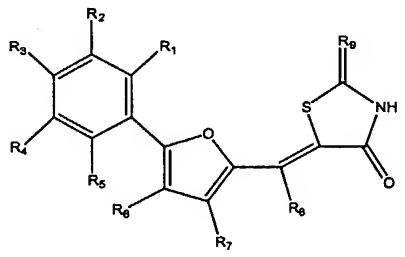
There is a further need in the art for methods of preparing such compounds and bi-ligands. There is also a need in the art for methods of preparing combinatorial libraries of the bi-ligands and methods of screening these libraries to find bi-ligands that interact with a drug target with improved affinity and/or specificity. The present invention satisfies these needs and provides related advantages as well.

SUMMARY OF THE INVENTION

The present invention provides compounds that function as mimics to a natural common ligand for a receptor family. These compounds interact with a conserved binding site on multiple receptors within the receptor family.

In one aspect, the present invention provides compounds that are common ligand mimics for NAD. NAD is a natural common ligand for many oxidoreductases. Thus, compounds of the invention that are common ligand mimics for NAD interact selectively with conserved sites on oxidoreductases.

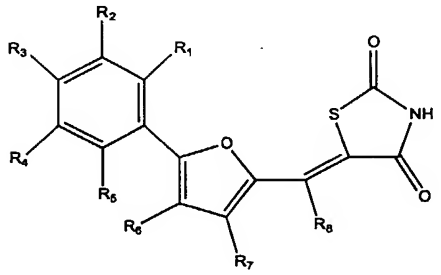
In one embodiment, the present invention provides compounds of Formula I,



wherein R_1 to R_8 each independently are H, alkyl, alkenyl, alkynyl, aryl, heterocycle, COOH, COOAlkyl, $CONR_{10}R_{11}$, $C(O)R_{12}$, OH, OAlkyl, OAc, SH, SR_{12}, SO_3H, $S(O)R_{12}$, $SO_2NR_{10}R_{11}$, $S(O)_2R_{12}$, NH_2, NHR_{12}, $NR_{10}R_{11}$, $NHCOR_{12}$, $NR_{10}COR_{12}$, N_3, NO_2, PH_3, PH_2R_{12}, H_2PO_4, H_2PO_3, H_2PO_2, HPO_4R_{12}, $PO_2R_{11}R_{12}$, CN, or X. R_9 is an oxygen, sulfur, or nitrogen atom, where the nitrogen atom can be substituted, e.g. NR_{12}; and

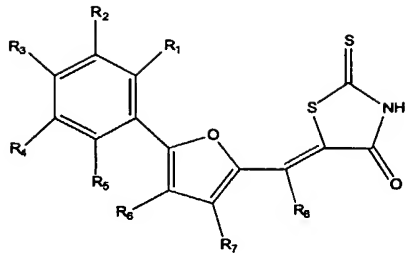
R_{10}, R_{11}, and R_{12} each independently are hydrogen, alkyl, alkenyl, alkynyl, aryl, or heterocycle, or R_{10} and R_{11} together with the nitrogen to which they are attached can be joined to form a heterocyclic ring.

In another embodiment, the invention provides thiazolidinedione compounds of Formula II,



wherein R_1 to R_8 each independently are H, alkyl, alkenyl, alkynyl, aryl, heterocycle, COOH, COOAlkyl, $CONR_{10}R_{11}$, $C(O)R_{12}$, OH, OAlkyl, OAc, SH, SR_{12}, SO_3H, $S(O)R_{12}$, $SO_2NR_{10}R_{11}$, $S(O)_2R_{12}$, NH_2, NHR_{12}, $NR_{10}R_{11}$, $NHCOR_{12}$, $NR_{10}COR_{12}$, N_3, NO_2, PH_3, PH_2R_{12}, H_2PO_4, H_2PO_3, H_2PO_2, HPO_4R_{12}, $PO_2R_{11}R_{12}$, CN, or X. R_{10}, R_{11}, and R_{12} each independently are hydrogen, alkyl, alkenyl, alkynyl, aryl, or heterocycle, or R_{10} and R_{11} together with the nitrogen to which they are attached can be joined to form a heterocyclic ring.

In still another embodiment, the invention provides rhodanine compounds of Formula III,



wherein R_1 to R_8 each independently are H, alkyl, alkenyl, alkynyl, aryl, heterocycle, COOH, COOAlkyl, $CONR_{10}R_{11}$, OH, OAlkyl, OAc, SH, SR_{12}, SO_3H, $S(O)R_{12}$, $SO_2NR_{10}R_{11}$, $S(O)_2R_{12}$, NH_2, NHR_{12}, $NR_{10}R_{11}$, $NHCOR_{12}$, $NR_{10}COR_{12}$, N_3, NO_2, PH_3, PH_2R_{12}, H_2PO_4, H_2PO_3, H_2PO_2, HPO_4R_{12}, $PO_2R_{11}R_{12}$, CN, or X. R_{10}, R_{11}, and R_{12} each independently are hydrogen, alkyl, alkenyl, alkynyl, aryl, or heterocycle, or R_{10} and R_{11} together with the nitrogen to which they are attached can be joined to form a heterocyclic ring.

In a second aspect, the present invention provides methods for preparing compounds of Formula I. These methods generally comprise two steps. In the first step of each method, a furaldehyde intermediate is formed. In the second step, the furaldehyde intermediate is reacted either with 2,4-thiazolidinedione to form a compound of Formula II or with rhodanine to form a compound of Formula III.

In a third aspect, the present invention provides bi-ligands containing a common ligand mimic and a specificity ligand which interact with distinct sites on a receptor. In one embodiment, the present invention provides bi-ligands that are the reaction products of

compounds of Formula I with specificity ligands. In another embodiment, the invention provides bi-ligands containing the reaction products of compounds of Formula II with specificity ligands. In yet another embodiment, the invention provides bi-ligands that are reaction products of compounds of Formula III and specificity ligands. In yet another aspect, the invention provides methods for preparing bi-ligands that are reaction products of the common ligand mimics of general Formulas I, II, and III and a pyridine dicarboxylate specificity ligand.

The present invention further provides combinatorial libraries containing one or more common ligand variants of the compounds of the invention. In one embodiment, the combinatorial libraries of the invention contain one or more common ligand variants of the compounds of Formula I. In other embodiments, the combinatorial libraries of the invention contain one or more common ligand variants of the compounds of Formula II or Formula III.

The present invention also provides combinatorial libraries comprised of one or more bi-ligands that are reaction products of common ligand mimics and specificity ligands. In one embodiment, such combinatorial libraries contain one or more bi-ligands that are the reaction product of compounds of Formula I and specificity ligands. In another embodiment, such combinatorial libraries contain one or more bi-ligands that are the reaction product of compounds of Formula II and specificity ligands. In still another embodiment,

such combinatorial libraries contain one or more bi-ligands that are the reaction product of compounds of Formula III and specificity ligands.

The present invention also provides methods for producing and screening combinatorial libraries of bi-ligands for binding to a receptor and families of such receptors.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows Scheme 1 for the synthesis of thiazolidinedione compounds of Formula II where R_1 to R_8 each independently are H, alkyl, alkenyl, alkynyl, aryl, heterocycle, COOH, COOAlkyl, $CONR_{10}R_{11}$, $C(O)R_{12}$, OH, OAlkyl, OAc, SH, SR_{12}, SO_3H, $S(O)R_{12}$, $SO_2NR_{10}R_{11}$, $S(O)_2R_{12}$, NH_2, NHR_{12}, $NR_{10}R_{11}$, $NHCOR_{12}$, $NR_{10}COR_{12}$, N_3, NO_2, PH_3, PH_2R_{12}, H_2PO_4, H_2PO_3, H_2PO_2, HPO_4R_{12}, $PO_2R_{11}R_{12}$, CN, or X. R_{10}, R_{11}, and R_{12} each independently are hydrogen, alkyl, alkenyl, alkynyl, aryl, or heterocycle, or R_{10} and R_{11} together with the nitrogen to which they are attached can be joined to form a heterocyclic ring. The reaction steps are as follows: (a) an aminobenzoic acid and 2-furaldehyde are reacted in the presence of HNO_2 and $CuCl_2/CuCl$ to form a furaldehyde intermediate; (b) the furaldehyde intermediate is reacted with 2,4-thiazolidinedione, while heating, to form the corresponding thiazolidinedione.

Figure 2 shows Scheme 1 for the synthesis of rhodanine compounds of Formula III where R_1 to R_8 each independently are H, alkyl, alkenyl, alkynyl, aryl, heterocycle, COOH, COOAlkyl, $CONR_{10}R_{11}$, $C(O)R_{12}$, OH,

OAlkyl, OAc, SH, SR_{12}, SO_3H, $S(O)R_{12}$, $SO_2NR_{10}R_{11}$, $S(O)_2R_{12}$, NH_2, NHR_{12}, $NR_{10}R_{11}$, $NHCOR_{12}$, $NR_{10}COR_{12}$, N_3, NO_2, PH_3, PH_2R_{12}, H_2PO_4, H_2PO_3, H_2PO_2, HPO_4R_{12}, $PO_2R_{11}R_{12}$, CN, or X. R_{10}, R_{11}, and R_{12} each independently are hydrogen, alkyl, alkenyl, alkynyl, aryl, or heterocycle, or R_{10} and R_{11} together with the nitrogen to which they are attached can be joined to form a heterocyclic ring.. The reaction steps are as follows: (a) an aminobenzoic acid and 2-furaldehyde are reacted in the presence of HNO_2 and $CuCl_2/CuCl$ to form a furaldehyde intermediate; (b) the furaldehyde intermediate is reacted with rhodanine, while heating, to form the corresponding rhodanine compound.

Figure 3 shows Scheme 2 for the synthesis of thiazolidinedione compounds of Formula II where R_1 to R_8 each independently are H, alkyl, alkenyl, alkynyl, aryl, heterocycle, COOH, COOAlkyl, $CONR_{10}R_{11}$, $C(O)R_{12}$, OH, OAlkyl, OAc, SH, SR_{12}, SO_3H, $S(O)R_{12}$, $SO_2NR_{10}R_{11}$, $S(O)_2R_{12}$, NH_2, NHR_{12}, $NR_{10}R_{11}$, $NHCOR_{12}$, $NR_{10}COR_{12}$, N_3, NO_2, PH_3, PH_2R_{12}, H_2PO_4, H_2PO_3, H_2PO_2, HPO_4R_{12}, $PO_2R_{11}R_{12}$, CN, or X. R_{10}, R_{11}, and R_{12} each independently are hydrogen, alkyl, alkenyl, alkynyl, aryl, or heterocycle, or R_{10} and R_{11} together with the nitrogen to which they are attached can be joined to form a heterocyclic ring. The reaction steps are as follows: (a) a halobenzoate and 5-trimethylstannanyl-furan-2-carbaldehyde are reacted in the presence of $Pd(PPh_3)_4$ to form a furaldehyde intermediate; (b) the furaldehyde intermediate is reacted with 2,4-thiazolidinedione while heating, to form the corresponding thiazolidinedione.